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PATENT SPECIFICATION

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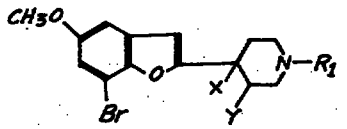
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(54) TETRAHYDROPYRIDINE AND PIPERIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

(71) We, CIBA - GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to tetrahydropyridine and piperidine derivatives having valuble pharmacological properties, to processes for the production of these compounds, as well as to therapeutic preparations containing them.

The tetrahydropyridine and piperidine derivatives according to the invention correspond to the general formula I



(I)

wherein

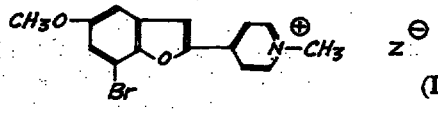
R_1 represents hydrogen or methyl, and X and Y each represent hydrogen, or, if R_1 is methyl, together can represent an additional bond.

The invention likewise relates to addition salts, especially to pharmaceutically acceptable addition salts of the compounds of the general formula I with inorganic and organic acids, as well as to the production of these addition salts.

The compounds of the general formula I, 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydropyridine, 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methylpiperidine and 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine, and their addition salts with inorganic and organic acids possess valuable pharmacological properties. As is shown by the results of the isotopic determination of the enzyme activity, they inhibit in the rat and in other species of experimental animals mono - amine oxidase, in particular selectively and reversibly the A-form thereof, after oral or subcutaneous administration of doses down to 1.0 mg/kg in the case of the first- and second-mentioned compounds, whilst the last-mentioned compound is effective even in doses down to 0.1 mg/kg. At the same time, the compounds of the general formula I exhibit in the rat, in comparison with the very strong MAO-A inhibition, also a less pronounced inhibition of the absorption of noradrenaline into the heart after oral or subcutaneous administration of doses of 10 to 100 mg/kg, and inhibit also the absorption of serotonin into the midbrain synaptosomes of rats. Furthermore, they antoganise, in the case of intraperitoneal administration of doses of 2 to 40 mg/kg, the hypothermal action of reserpine in the rat. Together with a favourable therapeutic index, the above-mentioned properties characterise the compounds of the general formula I and their pharmaceutically acceptable salts with inorganic and organic acids as antidepressants which, for example, can be administered orally or parenterally for the treatment of mental depression.

The tetrahydropyridine and piperidine derivatives of the general formula I and their acid addition salts are produced according to the invention by a process in which, in a manner known *per se*,

a) a compound of the general formula II



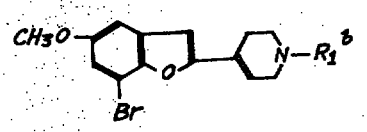
(II)

wherein

$Z^{\ominus}$ represents a monovalent anion or the normal equivalent of a polyvalent anion, is partially reduced to the corresponding com-

pound of the general formula I wherein R_1 represents methyl, and X and Y together represent an additional bond; or

b) a compound of the general formula III



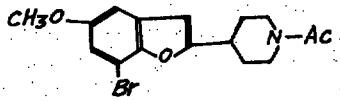
(III)

wherein

R_1^b represents methyl or benzyl, in the benzene ring of which at most three hydrogen atoms can be replaced with substituents selected from halogen up to atomic number 35, lower alkyl groups and lower alkoxy groups, methylenedioxy groups and trifluoromethyl groups,

is catalytically hydrogenated to give a compound of the general formula I wherein R_2 represents methyl or hydrogen, and X and Y each represent hydrogen; or

c) in a compound of the general formula IV



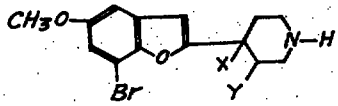
(IV)

wherein

Ac represents a radical which can be split off,

the radical Ac is split off; or

d) a compound of the general formula V

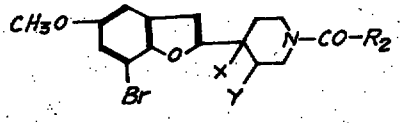


(V)

wherein

X and Y have the meaning given under the formula I, is reacted with a reactive ester of methanol, or with formaldehyde under reducing conditions; or

e) in a compound of the general formula VI



(VI)

wherein

R_2 represents hydrogen or lower alkoxy, and

X and Y have the meaning given under the formula I, the formyl or alkoxycarbonyl group is reduced;

and, optionally, a compound of the general formula I obtained by any one of the processes defined under a) to e) is converted into an addition salt with an inorganic or organic acid.

Throughout this specification, the term "lower" is used to denote that a radical or compound has up to 4 carbon atoms.

The partial reduction of a compound of the general formula II according to a) is preferably performed with the aid of sodium or potassium borohydride in an organic-aqueous medium by a process wherein, for example, there is slowly added to the solution of the starting material of the general formula II in an organic solvent miscible with water, e.g. in a lower alkanol such as methanol or ethanol or in a mixture thereof with water, an aqueous solution of sodium borohydride, and the reaction mixture is subsequently allowed to further react for some time, whereby a reaction temperature of between 5 and 60°C, preferably between room temperature and 35°C, is maintained. The production of the starting materials of the general formula II is described later in the text.

The catalytic hydrogenation of a compound of the general formula III according to b) can be performed with the use of a customary hydrogenation catalyst, for example a noble metal catalyst such as palladium on charcoal or platinum oxide, a rhodium catalyst such as rhodium on charcoal or on aluminium oxide, or an alloy-skeleton catalyst such as Raney nickel, in an inert organic solvent such as methanol, ethanol or dioxane, and optionally with the addition of hydrobromic acid, at room temperature and normal pressure, or at a moderately elevated temperature up to 100°C and at an elevated pressure up to 100 bars. If R_1^b in the starting material is methyl, the hydrogenation is terminated after absorption of the equimolar amount of hydrogen; and if R_1^b is a benzyl group optionally substituted as defined, which is to be replaced with hydrogen, i.e. is to be hydrogenolytically split off, it is terminated after absorption of the double-molar amount of hydrogen. The starting material of the general formula III having a methyl group as R_1^b is embraced by the general formula I and can be produced for example by process a). The further compounds of the general formula I can be produced, e.g., analogously to process a) with the use of corresponding starting materials which contain on the quaternary nitrogen atom, instead of the methyl group, a benzyl group optionally substituted as defined.

In the starting materials of the general formula IV, the radical Ac which can be split off is, in particular, an acyl radical. It is split off, for example, by hydrolysis, solvolysis, hydrogenolysis or reduction. In the starting materials of the general formula IV, Ac can be for example any desired organic acyl group, e.g. a lower alkanoyl group such as an acetyl group, an arenecarbonyl group such as the benzoyl group, an alkanesulphonyl group or arenesulphonyl group, such as a methanesulphonyl group or a *p* - toluenesulphonyl group. However, acyl groups are preferred which ensure the easy obtainment of the compounds of the general formula IV

which contain them and/or which are relatively easily split off. Accordingly, therefore, preferred acyl groups Ac on the one hand are, in particular, acyl groups of semi-esters of carbonic acid and thiocarbonic acid, especially groups that can be split off by hydrolysis, e.g. lower alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl and tert.-butoxycarbonyl groups, also phenoxycarbonyl and benzyloxycarbonyl groups, as well as methoxythiocarbonyl and methylthio - thiocarbonyl groups; and on the other hand acyl groups of further derivatives of carbonic acid, such as a chlorocarbonyl group and, in particular, a cyano group.

The hydrolysis of compounds of the general formula IV according to process c) can be performed in an alkaline or acid medium. It is performed, for example, by prolonged heating with an alkali hydroxide, especially with sodium or potassium hydroxide, in a hydroxy compound in the presence of a little water at a temperature of between 80° and 200°C. A suitable reaction medium is, for example, ethylene glycol or a lower monoalkyl ether thereof and, with performance of the hydrolysis in a closed vessel, also a lower alkanol such as methanol, ethanol or butanol. Furthermore, in particular the compound of the general formula IV wherein Ac represents a cyano group, i.e. the acyl radical of cyanic acid, or a chlorocarbonyl group, can be hydrolysed also by being heated with a mineral acid in an organic-aqueous or aqueous medium, e.g. by several hours' boiling in a mixture of 85% phosphoric acid and formic acid, or by several hours' heating in 48% hydrobromic acid or in a mixture of hydrobromic acid and acetic acid at 60—100°C, preferably 60—70°C, or by boiling in dilute hydrochloric acid, e.g. in 0.5N hydrochloric acid.

A radical that can be split off by solvolysis is, for example, a tert.butoxycarbonyl radical, which can be split off under anhydrous conditions by treatment with a suitable acid, such as trifluoroacetic acid.

Acyl radicals Ac that can be split off by reduction are, for example, α - aralkoxycarbonyl radicals, such as benzyloxycarbonyl radicals, which can be split off in the usual manner by hydrogenolysis, particularly by catalytically activated hydrogen, such as by hydrogen in the presence of a hydrogenation catalyst, for example platinum, palladium or Raney nickel. Further radicals that can be split off by reduction are, for example 2 - haloalkoxycarbonyl radicals, such as the 2,2,2 - trichloroethoxycarbonyl radical or the 2 - iodoethoxy- or 2,2,2 - tribromoethoxycarbonyl radical, which can be split off in the usual manner, especially by metallic reduction (so-called nascent hydrogen). Nascent hydrogen can be obtained by the action of metal, or metal alloys such as amalgams, on hydrogen - releasing agents, such as carboxylic acids, alcohols or water, whereby, in particular, zinc or zinc alloys together with acetic acid are suitable. The reduction of 2 - halogen - alkoxycarbonyl radicals can also be performed by means of chromium(II) - compounds, such as chromium(II) - chloride or chromium(II) - acetate.

A radical Ac that can be split off by reduction can also be a sulphonyl group, such as a lower alkanesulphonyl group or arylsulphonyl group, such as methanesulphonyl or *p* - toluenesulphonyl, which can be split off in the usual manner by reduction with nascent hydrogen, e.g. by an alkali metal such as lithium or sodium, in liquid ammonia, or can be split off electrolytically.

The production of the starting materials of the general formula IV is described later in the text.

Suitable reactive esters of methanol for the reaction with compounds of the general formula V according to the process d) are, for example: hydrohalic acid esters, especially bromide or iodide, also lower alkanesulphonic acid esters and arenesulphonic acid esters, such as methanesulphonic acid esters, or benzenesulphonic acid esters and *p* - toluenesulphonic acid esters, as well as esters of other strong acids, e.g. the sulphuric acid ester, i.e. dimethylsulphate. The reactions with compounds of the general formula V are preferably performed in the presence of an acid-binding agent in an organic solvent inert under the reaction conditions. Preferred acid-binding agents are tertiary organic bases, such as triethylamine, pyridine, *sym.* collidine and, in particular, ethyldiisopropylamine, or inorganic basic substances such as sodium carbonate or potassium carbonate; and suitable solvents are, e.g., lower alkanols such as methanol, ethanol, isopropanol or butanol, ethereal compounds such as dioxane, tetrahydrofuran or 2 - methoxy - ethanol, lower aliphatic ketones such as methyl ethyl ketone, and N - substituted acid amides such as dimethylformamide or N,N,N',N',N'',N''-hexamethylphosphoric acid triamide. The reaction temperature is between 0° and 200°C, preferably between room temperature and 120°C.

Reactions of compounds of the general formula V with formaldehyde can be performed, for example, in formic acid at a temperature of between 70 and 100°C; optionally also by the action of hydrogen in the presence of a hydrogenation catalyst, such as Raney nickel, platinum oxide or palladium charcoal, at normal or moderately elevated pressures and temperatures, in a suitable organic solvent such as ethanol or dioxane. Of the compounds of the general formula V, that with hydrogen atoms as X and Y is embraced by the general formula I, and can be produced, for example, according to process b) or c). Analogously to process c) can also be produced the compound of the general formula V having an

additional bond as X and Y from corresponding starting materials which, for their part, are obtainable fully analogously to those of the general formula IV.

The reduction of the formyl or lower alkoxycarbonyl group of compounds of the general formula VI according to e) to the methyl group is performed, for example, by means of lithium aluminium hydride or diborane in an ethereal solvent, such as diethyl ether, tetrahydrofuran, dibutyl ether or diethylene glycol diethyl ether, or in mixtures thereof, at a temperature of between 20 and 100°C, or at the boiling temperature of the employed reaction medium; where this temperature is below 100°C. The diborane can be either prepared separately and introduced, or formed in situ from sodium borohydride and boron trifluoride etherate. The production of the starting materials of the general formula VI is described later in the text.

The starting materials for the above-mentioned processes which are not already embraced by the general formula I and which have not already received particular mention can be produced, in one or more stages, from 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - pyridine. This copound can in its turn be produced, for example, by reacting 3 - bromo - 5 - methoxysalicylaldehyde with a 4 - (halogenomethyl) - pyridine, particularly 4 - (chloromethyl)- or 4 - (bromomethyl) - pyridine, in the presence of an acid-binding agent such as potassium carbonate, as well as, optionally, sodium iodide or potassium iodide, with heating in an organic solvent such as dimethylformamide, whereby in addition to the ether formation to the intermediate 2 - [(4 - pyridyl) - methoxy] - 3 - bromo - 5 - methoxybenzaldehyde there also occurs, with the elimination of water, the formation of the benzofuran ring.

From 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - pyridine is obtained, in a manner known *per se*, by quaternisation with a reactive ester of methanol, e.g. one of those mentioned in connection with process d), a compound of the general formula II. Quaternisation can be performed in the usual manner in an inert organic solvent, e.g. in methanol, ethyl methyl ketone, ethyl acetate, tetrahydrofuran or dioxane, at room temperature or at moderately elevated temperatures up to 100°C.

By quaternisation of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - pyridine with a reactive ester of a benzyl alcohol, or of a benzyl alcohol substituted according to the definition for R_1" given under formula III, there is obtained in an analogous manner a quaternary pyridinium compound which contains, instead of the methyl group, an optionally substituted benzyl group and which, as already mentioned, can be reduced analogously to process a) to a starting material of the general formula III for the process b).

Starting materials of the general formula IV in which Ac is the acyl radical of a carbonic acid semi-ester or thiocarbonic acid semi-ester, or a cyano radical or a chlorocarbonyl radical, can be produced, for example, from 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine embraced by the general formula I, or from an analogous compound containing, instead of the methyl group, another group readily split off, such as the allyl or benzyl group by reaction with a chloroformic acid ester or a chloroformic acid thio-ester, particularly with chloroformic acid ethyl ester, chloroformic acid *tert.*butyl ester, chloroformic acid benzyl ester of chloroformic acid phenyl ester, or with chlorothioformic acid - S - methyl ester, or with cyanogen bromide or phosgene, in an inert organic solvent at elevated temperature, e.g. in toluene or benzene at the boiling temperature thereof. Instead of using one of the aforementioned carbonic acid derivatives, it is also possible to use, e.g., a carboxylic acid halide such as acetyl bromide or benzoyl chloride, but the corresponding reaction for splitting off the methyl group or another group which can be split off usually requires more energetic conditions and is less complete than, e.g., with the use of chloroformic acid ethyl ester and, in particular, cyanogen bromide.

Starting materials of the general formula VI with hydrogen as X and Y are obtained, for example, in a manner known *per se* from 4 - (7 - bromo - 5 - methoxy 2 - benzofuranyl) - piperidine by reaction with formic acid/acetic acid anhydride at room temperature or at moderately elevated temperatures up to 100°C, preferably at 50°C, or by heating with a formic acid lower alkyl ester, especially with formic acid methyl ester, or reaction with a chloroformic acid lower alkyl ester, particularly chloroformic acid methyl ester or chloroformic acid ethyl ester, in the presence of an acid-binding agent such as potassium carbonate, in an inert organic solvent such as dioxane, or in pyridine or mixtures thereof with an inert organic solvent, at moderately elevated temperatures. Starting materials of the general formula VI with hydrogen as X and Y, and lower alkoxy, especially ethoxy or methoxy, as R_2, can be obtained, e.g., from corresponding compounds having a radical, which is readily split off, in the 1 - position, such as 1 - allyl- or 1 - benzyl - 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine, by reaction with chloroformic acid lower alkyl esters in the manner given for the production of compounds of the general formula IV. In an analogous manner it is possible to produce from 1 - benzyl - 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1,2,3,6 - tetrahydropyridine embraced by the general formula III, or from the corresponding 1 -

allyl or 1 - methyl compound, compounds of the general formula VI having an additional bond as X and Y, and lower alkoxy as R_2.

Depending on the conditions of the process and on the starting materials, the starting materials are obtained in the free form, or in the form, likewise included in the invention, of their acid addition salts. The acid addition salts of the compounds of the general formula I can be converted in a known manner into the free bases, e.g. with basic agents such as alkalies or ion exchangers. On the other hand, the compounds of the general formula I obtained by the process according to the invention can, optionally, be converted in the usual manner into their addition salts with inorganic or organic acids. For example, the acid desired as salt component is added to a solution of a compound of the general formula I in an organic solvent. Solvents preferably used for the reaction are those in which the occurring salt is difficultly soluble, so that the salt can be separated by filtration. Such solvents are, for example, ethyl acetate, methanol, ether, acetone, ethyl methyl ketone, acetone/ether, acetone/ethanol, methanol/ether or ethanol/ether.

The invention also provides a pharmaceutical preparation for the treatment of mental depression, which preparation comprises a compound of the general formula I, or a pharmaceutically acceptable acid addition salt thereof, in admixture or conjugation with a pharmaceutically suitable carrier.

It is possible to use as pharmaceutically active substances, instead of free bases, pharmaceutically acceptable acid addition salts, i.e. salts with acids of which the anions are not toxic in the dosage amounts concerned. Moreover, it is of advantage if the salts to be used as pharmaceutically active substances readily crystallise and are not, or are only slightly, hygroscopic. For salt formation with compounds of the general formula I, it is possible to use, e.g., hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, 2 - hydroxyethanesulphonic acid, acetic acid, lactic acid, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid.

The active substances of the invention are administered orally, rectally or parenterally. The dosage amounts depend on the mode of administration, on the species, on the age and on the individual condition. The daily doses of a free base or of a pharmaceutically acceptable acid addition salt of a free base vary between 0.01 mg/kg and 1.0 mg/kg for warm-blooded animals. Suitable dosage units, such as dragées, tablets, suppositories or ampoules, preferably contain 0.5—10 mg of an active substance according to the invention.

Dosage units for oral administration contain as active substance preferably between 0.5 and 10% of a compound of the general formula I, or of a pharmaceutically acceptable salt thereof. The said dosage units are produced by combination of the active substance with, e.g., a solid pulverulent carrier, such as lactose, saccharose, sorbitol or mannitol; a starch such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; a cellulose derivative or gelatine, optionally with the addition of a lubricant, such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The dragée cores are coated, for example, with a concentrated sugar solution which can also contain, e.g., gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in a readily volatile organic solvent or solvent mixture. A dyestuff can be added to these coatings, e.g. for identification of the various dosage amounts.

Further suitable oral dosage units are hard gelatine capsules, as well as soft closed capsules made from gelatine and a softener such as glycerin. The hard gelatine capsules contain the active substance preferably as a granulate, e.g. in admixture with a filler such as maize starch, and/or a lubricant such as talcum or magnesium stearate, and optionally a stabiliser such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in a suitable liquid, such as in a polyethylene glycol, whereby likewise a stabiliser may be added.

Suitable dosage units for rectal administration are, e.g., suppositories consisting of a combination of an active substance with a suppository foundation substance. Suppository foundation substances which can be used are e.g., natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Also suitable are gelatine rectal capsules consisting of a combination of the active substance with a foundation substance. Suitable foundation substances are, e.g., liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Ampoules for parenteral administration, especially intramuscular administration, preferably contain a water-soluble salt of an active substance in a concentration preferably of from 0.1 to 2%, optionally together with a suitable stabiliser and/or buffer substance, in aqueous solution.

The following examples further illustrate the production of tablets, dragées, capsules, suppositories and ampoules:

a) 25.0 g of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine hydrochloride is mixed with 300.80 g of lactose and 269.70 g of potato starch; the mixture is moistened with an alcoholic solution of 10 g of stearic acid, and then granulated through

a sieve. After drying of the granulate, 160 g of potato starch, 200 g of talcum, 2.50 g of magnesium stearate and 32 g of colloidal silicon dioxide are mixed in, and the mixture is subsequently pressed out to form 10,000 tablets each weighing 100 mg and each containing 2.5 mg of active substance; if required, the tablets can be provided with grooves to obtain a more precise adjustment of the dosage amount.

b) A granulate is prepared from 50.0 g of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 4 - methyl - piperidine hydrochloride, 175.90 g of lactose and the alcoholic solution of 10 g of stearic acid; after drying, the granulate is mixed with 56.60 g of colloidal silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate, and the mixture is subsequently pressed out to form 10,000 dragée cores. There are afterwards coated with a concentrated syrup prepared from 502.28 g of cryst. saccharose, 6 g of shellac, 10 g of gum arabic, 0.22 g of dyestuff and 1.5 g of titanium dioxide, and finally dried. The dragées obtained each weigh 100 mg and each contain 5 mg of active substance.

c) To produce 1000 capsules each containing 1.0 mg of active substance, 1.0 g of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine hydrochloride is mixed with 2.57 g of lactose; the mixture is uniformly moistened with an aqueous solution of 2 g of gelatine, and then granulated through a suitable sieve (e.g. of 1.2 mm mesh size). The granulate is mixed with 10.0 g of dried maize starch and 15.0 g of talcum, and the mixture is evenly filled into 1000 hard gelatine capsules, size 1.

d) A suppository mixture is prepared from 1.0 g of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydropyridine hydrochloride and 169.0 g of adeps solidus, and the mixture is used to pour 100 suppositories each containing 10 mg of active substance.

e) a solution of 2.0 g of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine hydrochloride in one litre of water is filled into 1000 ampoules, and then sterilised. An ampoule contains a 0.2% solution of 2.0 mg of active substance.

The following Examples further illustrate the production of the new compounds of the general formula I and of intermediates not hitherto described; these Examples however are in no way intended to limit the scope of the invention. Temperatures are expressed in degrees Centigrade.

Example 1

A solution of 10.7 g of sodium borohydride in 60 ml of water is added dropwise, with stirring and external cooling, to a solution of 31.2 g (0.07 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - pyridinium iodide in 200 ml of methanol, the addition being made in such a manner that the reaction temperature does not exceed 35°. The solution is subsequently stirred for 20 hours at room temperature. The methanol is thereupon evaporated off in vacuo; the aqueous phase remaining is extracted twice with 500 ml of chloroform each time; the chloroform solution is dried over sodium sulphate, filtered and concentrated by evaporation. The residue is crystallised from methanol/water to obtain 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydropyridine, m.p. 73—77°. The hydrochloride prepared therefrom with a solution of hydrogen chloride in ether/tetrahydrofuran melts at 247—250° after recrystallisation from ethanol.

The starting material can be produced in the following manner:

a) 75.5 g (0.327 mole) of 3 - bromo - 5 - methoxysalicylaldehyde, 53.6 g (0.327 mole) of 4 - (chloromethyl) - pyridine hydrochloride, 194 g of potassium carbonate and 15 g of potassium iodide in 320 ml of dimethylformamide are heated under nitrogen at 150° for 20 hours. The reaction mixture is thereupon cooled to about 50° and at this temperature filtered with suction. The filter residue is heated with 200 ml of dimethylformamide to 100° and filtered off with suction; and the new filter residue is subsequently washed with dimethylformamide. The combined filtrates are concentrated in vacuo, and the residue is subsequently freed from volatile constituents by heating for 2 hours at 80° in a high vacuum. The residue is dissolved in a small amount of methylene chloride, and chromatographed in 800 g of aluminium oxide (activity II, neutral). The first fraction, eluted with 2 litres of chloroform, is 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - pyridine, which melts at 149—152° after recrystallisation from ethyl acetate.

b) 23.4 g (0.767 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - pyridine is dissolved in 470 ml of ethyl methyl ketone, and stirred with 11.5 ml of methyl iodide for 15 hours at about 50°. The solution is thereupon cooled to −6° and the precipitated salt is filtered off with suction. The filter residue is subsequently washed with ether petroleum ether. The resulting 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - pyridinium iodide melts at 260—265° and can be directly further processed.

Example 2

25.1 g (0.078 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydropyridine is dissolved in 970 ml of methanol, and the solution is hydrogenated in the presence of 1.2 g of platinum

dioxide catalyst and 13.1 g of 48% aqueous hydrobromic acid at a temperature of between 20 and 25° under normal pressure until about 100% of the theoretically required amount of hydrogen has been absorbed. Hydrogenation is terminated, the catalyst is filtered off and the filtrate is concentrated in vacuo. The residue is distributed between ethyl acetate and aqueous 2N ammonia solution; the ethyl acetate phase is separated, washed with saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated by evaporation. The residue is distilled in high vacuum (molecular distillation). The fraction passing over at 180—200° and 0.1 torr is 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine. The hydrochloride prepared from a solution of the base with a solution of hydrogen chloride in ethyl methyl ketone melts at 231—234°.

Example 3

13.0 g (0.04 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine is dissolved in 240 ml of toluene. 20.7 g of chloroformic acid ethyl ester is slowly added dropwise, and under a strong flow of nitrogen to effect a more rapid removal of the liberated methyl chloride. The solution is thereupon stirred for 20 hours at 60°; it is then cooled, filtered with suction, and the filter residue is subsequently washed with 240 ml of toluene. The combined filtrates are successively washed with 250 ml of water, 250 ml of a 10% solution of methanesulphonic acid in water, 250 ml of water, 250 ml of water, 250 ml of 2N sodium hydroxide solution and 500 ml of water; they are then dried over sodium sulphate, filtered and concentrated by evaporation. The 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - piperidinecarboxylic acid ethyl ester remaining is an oil which is pure according to thin-layer chromatography an can be further processed without additional purification.

7.6 g (about 0.02 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - piperidinecarboxylic acid ethyl ester is dissolved in 80 ml of ethylene glycol. After the addition of 19.4 g of 86% potassium hydroxide, the formed cloudy solution is heated, with vigorous stirring, at 160° for 18 hours. The reaction solution is afterwards cooled to 100°, diluted with 80 ml of toluene and then cooled to 20°. The organic phases are extracted firstly twice with one litre of water each time and then four times with 200 ml of a 10% solution of methanesulphonic acid in water each time. The pH value of the methanesulphonic acid solution is adjusted to 12 by the addition of a 30% sodium hydroxide solution, and the solution is extracted with one litre of chloroform. The chloroform solution is dried with sodium sulphate, filtered and concentrated by evaporation to yield 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine, which solidifies on cooling. The hydrochloride is prepared from the base with hydrogen chloride in methanol, and is recrystallised from methanol/ether, whereupon it melts at 242—243°.

Example 4

66.8 g (0.20 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - piperidinecarbonitrile is refluxed in 400 ml of 0.5N hydrochloric acid for 5 hours. The clear reaction solution is rendered alkaline with conc. aqueous ammonia solution, and extracted with ether. The combined ether extracts are washed with water, dried over sodium sulphate and concentrated in a water-jet vacuum. There is obtained 4 - (5 - methoxy - 7 - bromobenzofuranyl - 2) - piperidine as oil, which crystallises on standing, m.p. 66—68°. The 4 - (5 - methoxy - 7 - bromo - 2 - benzofuranyl) - piperidine - hydrochloride produced from the above base with methanolic hydrochloric acid is crystallised from methanol/ether, m.p. 242—243°.

The starting material can be produced as follows:

a) A solution of 31.6 g (0.299 mole) of cyanogen bromide in 500 ml of benzene is added dropwise, within 15 minutes at room temperature, to a solution of 88.0 g (0.272 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methylpiperidine in 1000 ml of benzene. The reaction mixture is subsequently refluxed for one hour. The reaction mixture is well washed with water and then extracted ice-cold with 2N hydrochloric acid. The combined extracts are dried over sodium sulphate and completely concentrated in a water-jet vacuum. The resulting 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - piperidinecarbonitrile crystallises on standing. It is recrystallised from ether/petroleum ether to obtain the pure substance, m.p. 94—96°.

Example 5

A solution of 0.8 g (0.00165 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - piperidinecarboxylic acid - 2,2,2 - trichloroethyl ester in a mixture of 7.2 ml of acetic acid and 0.8 ml of water is cooled to 5°, and to this solution is added portionwise, with stirring, 0.64 g of zinc powder. After two hours, the reaction mixture is filtered and the filtrate is concentrated by evaporation. The residue is distributed between 2N sodium hydroxide solution and methylene chloride. The organic phase is separated, washed with saturated sodium sulphate solution, dried over sodium sulphate and concentrated by evaporation. As residue is obtained 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine in the form of yellow oil. This is dissolved in ethyl acetate,

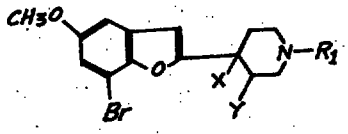
and ethereal hydrochloric acid is added until the mixture produces an acid reaction. It is then cooled, the formed crystals are filtered off with suction and washed with ether. The resulting 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine hydrochloride melts at 229—230°.

The starting material is produced as follows:

a) 1.0 g (0.0031 mole) of 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine is dissolved in 15 ml of toluene, and 1.97 g of chloroformic acid - 2,2,2 - trichloroethyl ester is slowly added. The mixture is then stirred for 21 hours at 70° under nitrogen and afterwards cooled. Toluene and water are added, the mixture is acidified with conc. hydrochloric acid, and the organic phase is separated. This is washed with water and conc. aqueous sodium chloride solution, dried over sodium sulphate and concentrated by evaporation. The oily residue is 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - piperidinecarboxylic acid - 2,2,2 - trichloroethyl ester, which can be further processed without additional purification.

WHAT WE CLAIM IS:—

1. A process for the production of a tetrahydropyridine or piperidine derivative of the general formula I



(I)

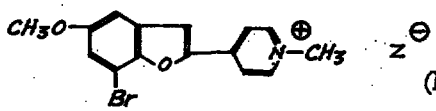
wherein

R_1 represents hydrogen or methyl, and

X and Y each represent hydrogen, or, if R_1 is methyl, together can represent an additional bond,

or an addition salt thereof with an inorganic or organic acid, in which process

a) a compound of the general formula II



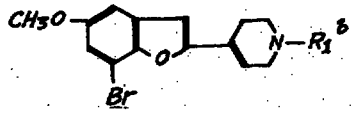
(II)

wherein

$Z^{\ominus}$ represents a monovalent anion or the normal equivalent of a polyvalent anion,

is partially reduced to the corresponding compound of the general formula I wherein R_1 represents methyl, and X and Y together represent an additional bond; or

b) a compound of the general formula III



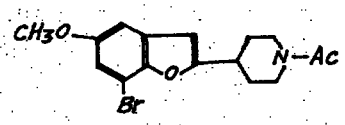
(III)

wherein

R_1^b represents methyl or benzyl, in the benzene ring of which at most three hydrogen atoms can be replaced with substituents selected from halogen up to atomic number 35, lower alkyl groups and lower alkoxy groups, the methylenedioxy group and the trifluoromethyl group,

is catalytically hydrogenated to a compound of the general formula I wherein R_1 represents methyl or hydrogen, and X and Y each represent hydrogen; or

c) in a compound of the general formula IV

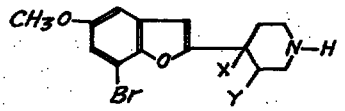


(IV)

wherein

Ac represents a radical which can be split off, the radical Ac is split off; or

d) a compound of the general formula V

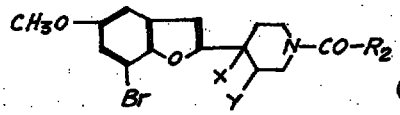


(V)

wherein

X and Y have the meaning given under formula I, is reacted with a reactive ester of methanol, or with formaldehyde under reducing conditions; or

e) in a compound of the general formula VI



(VI)

wherein

R_2 represents hydrogen or lower alkoxy, and

X and Y have the meaning given under the formula I, the formyl or alkoxycarbonyl group is reduced;

and, optionally, a compound of the general formula I obtained by any one of the processes defined under a) to e) is converted into an addition salt with an inorganic or organic acid.

2. A process according to Claim 1, wherein 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydropyridine or an acid addition salt is produced by one of the processes a), d) or e).

3. A process according to Claim 1, wherein 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine or an acid addition salt thereof is produced by one of the processes b), d) or e).

4. A process according to Claim 1, wherein 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine or an acid addition salt thereof is produced by one of the processes b) or c).

5. A compound of the general formula I

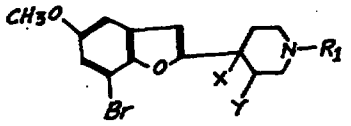
and ethereal hydrochloric acid is added until the mixture produces an acid reaction. It is then cooled, the formed crystals are filtered off with suction and washed with ether. The resulting 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine hydrochloride melts at 229—230°.

The starting material is produced as follows:

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WHAT WE CLAIM IS:—

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(I)

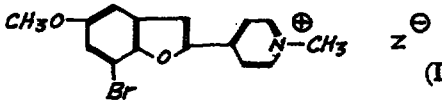
wherein

R_1 represents hydrogen or methyl, and

X and Y each represent hydrogen, or, if R_1 is methyl, together can represent an additional bond,

or an addition salt thereof with an inorganic or organic acid, in which process

a) a compound of the general formula II



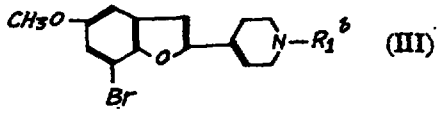
(II)

wherein

$Z^{\ominus}$ represents a monovalent anion or the normal equivalent of a polyvalent anion,

is partially reduced to the corresponding compound of the general formula I wherein R_1 represents methyl, and X and Y together represent an additional bond; or

b) a compound of the general formula III



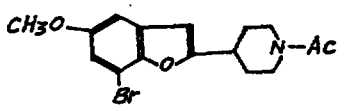
(III)

wherein

R_1^b represents methyl or benzyl, in the benzene ring of which at most three hydrogen atoms can be replaced with substituents selected from halogen up to atomic number 35, lower alkyl groups and lower alkoxy groups, the methylenedioxy group and the trifluoromethyl group,

is catalytically hydrogenated to a compound of the general formula I wherein R_1 represents methyl or hydrogen, and X and Y each represent hydrogen; or

c) in a compound of the general formula IV

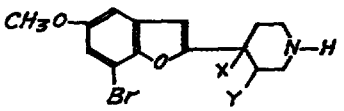


(IV)

wherein

Ac represents a radical which can be split off, the radical Ac is split off; or

d) a compound of the general formula V

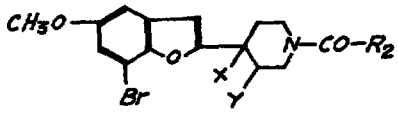


(V)

wherein

X and Y have the meaning given under formula I, is reacted with a reactive ester of methanol, or with formaldehyde under reducing conditions; or

e) in a compound of the general formula VI



(VI)

wherein

R_2 represents hydrogen or lower alkoxy, and

X and Y have the meaning given under the formula I, the formyl or alkoxycarbonyl group is reduced;

and, optionally, a compound of the general formula I obtained by any one of the processes defined under a) to e) is converted into an addition salt with an inorganic or organic acid.

2. A process according to Claim 1, wherein 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydropyridine or an acid addition salt is produced by one of the processes a), d) or e).

3. A process according to Claim 1, wherein 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine or an acid addition salt thereof is produced by one of the processes b), d) or e).

4. A process according to Claim 1, wherein 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine or an acid addition salt thereof is produced by one of the processes b) or c).

5. A compound of the general formula I

given in Claim 1, wherein R_1, X and Y have the meaning defined therein, and acid addition salts thereof.

6. 4 - (7 - Bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydro - pyridine and its acid addition salts.

7. 4 - (7 - Bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine and its acid addition salts.

8. 4 - (7 - Bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine and its acid addition salts.

9. A pharmaceutical preparation for the treatment of mental depression, which preparation comprises a compound of the general formula I given in Claim 1, wherein R_1, X and Y have the meaning defined therein, or pharmaceutically acceptable acid addition salt of a compound of the general formula I, in admixture or conjunction with a pharmaceutically suitable carrier.

10. A pharmaceutical preparation according to Claim 9 which comprises 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - 1,2,3,6 - tetrahydro - pyridine or a pharmaceutically acceptable acid addition salt thereof.

11. A pharmaceutical preparation according to Claim 9 which comprises 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - 1 - methyl - piperidine or a pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical preparation according to Claim 9 which comprises 4 - (7 - bromo - 5 - methoxy - 2 - benzofuranyl) - piperidine or a pharmaceutically acceptable acid addition salt thereof.

13. A process for the manufacture of a compound of the general formula I as claimed in claim 1, substantially as described in any one of Examples 1 to 5 herein.

14. A compound of the general formula I as defined in claim 1, whenever prepared by a process as claimed in any one of claims 1 to 4.

15. A pharmaceutical preparation as claimed in claim 9, substantially as described in any one of Examples a to e herein.

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